

Claim Objections

Claim 10 is objected to under 37 CFR 1.75 as being a duplicate of claim 9.

Applicants herein cancel claim 10 without prejudice.

Rejection under 35 U.S.C. §102

The Examiner rejects claims 1-34, 36-44 and 47-51 as anticipated by Heller *et al.*, U.S. Patent No. 5,929,208. The Examiner sets forth the following reasons for the rejection: The Examiner rejects claims 1 and 47 because Heller *et al.* allegedly disclose a method for electrochemical placement of a material at a specific location on a substrate, which comprises the steps of: providing a substrate having at its surface at least one electrode that is proximate at least one molecule bearing at least one protected chemical functional group (col. 17, lines 7-11); applying a potential to said electrode sufficient to generate electrochemical reagents capable of deprotecting at least one of the protected functional groups of said molecule and bonding the deprotected chemical at col. 20 lines 25-48. The Examiner says that the substrate may be of porous materials such as glass, silicon dioxide, plastic or ceramic materials (col. 10, lines 5-8) and more specifically CPG (col. 17, lines 7-9) consistent with those materials Applicant indicates on pages 27, lines 18-28; 28 line 18; 29, line 7 and 30, line 14 of the Specification.

The Examiner rejects claims 2, 18, 43 and 48 because Heller *et al.* allegedly disclose the placing of a buffer solution in contact with the electrode at the surface of the substrate to prevent electrochemically generated reagents from leaving the locality of the electrode (col. 22, lines 25-37).

The Examiner rejects claims 3, 19 and 49 are rejected because Heller *et al.* allegedly disclose the use of a phosphate buffer at col. 22, line 41. The Examiner rejects claims 4, 20 and 50 because the prior art allegedly discloses that the buffering solution is present in a concentration of at least 0.01 mM at col. 22, line 40. The Examiner rejects claims 5, 21 and 51 because the prior art allegedly discloses that the buffering solution is present in a concentration range of 0.1 to 100 mM at col. 22, line 40. The Examiner

rejects claim 6 because Heller allegedly discloses protected monomers or preformed molecules having protected chemical functional groups at non-bonding sites in col. 15, lines 48-58. The Examiner rejects claims 7 and 22 because Heller allegedly discloses amino acid as the monomer in col. 21, line 30. (Also see col. 6, lines 24-41.) The Examiner rejects claims 8 and 37 because Heller *et al.* allegedly employ pre-formed molecules selected from the group consisting of proteins, nucleic acids, polysaccharides and porphyrins (col. 17, lines 1-7). The Examiner rejects claims 9 (duplicate claim 10) and 23 because the reference allegedly discloses the use of linker molecules or monomers in col. 21, lines 10-16. The Examiner rejects claims 11 and 24 because the molecule of Heller *et al.* is allegedly directly attached to the surface of said substrate, via a linker molecule or attached to a layer of material overlaying said substrate in col. 14, lines 56-67.

Claims 12 and 27 are rejected because Heller *et al.* teach the protection of the chemical functional groups with an acid or base labile protecting group at col.

The Examiner rejects claims 13, 14, 29-31 and 40 as Heller *et al.* allegedly teach the use of an array of electrodes in col. 4, lines 44-54. While Heller *et al.* does not expressly recite the specific number of electrodes claimed, the Examiner says that the reference discloses the use of an array to allow for combinatorial synthesis and hybridization analysis in the 1000 to 100,000 copy range (col. 19, lines 38-40).

The Examiner rejects claim 15 as the combinatorial synthesis method of Heller *et al.* allegedly disclose sequentially deprotecting other protected chemical functional group of the monomer or pre-formed molecule and bonding another monomer or pre-formed molecule to the deprotected monomer in col. 15, lines 48-58. The Examiner rejects claim 16 as the method of Heller *et al.* allegedly further include bonding a second monomer and repeating the selective deprotection of a chemical functional group in col. 20, lines 25-49. The Examiner rejects claims 17 and 42 as the reference allegedly discloses selective deprotection by the application of potential to one or more electrodes sufficient to generate electrochemical reagents at the selected electrodes in col. 15, lines 48-58. The Examiner rejects claim 25 as Heller *et al.* allegedly disclose the use of CPG as protective overlayers

in col. 21, lines 31-35 of the reference. The Examiner rejects claim 26 as the reference allegedly also teaches a linker molecule comprising a group cleavable by an electrochemically generated reagent, which cleavable group enables removal from said substrate of one or more bonded molecules in col. 15, lines 48-52 and col. 16, lines 5-16. The Examiner rejects claim 28 as the substrate allegedly used in the prior art may be a semiconductor, plastic, glass or ceramic substrate in col. 10, lines 5-8.

Applicants explained some of the differences between the teachings of Heller *et al.* and the presently claimed invention in the present specification. Specifically, Applicants provided a summary of some of the differences at page 6, line 10 through page 7, line 12. Applicant explained that Heller *et al.* describe a self-addressable, self-assembling microelectronic system that can carry out controlled multi-step reactions in microscopic environments, including biopolymer synthesis of oligonucleotides and peptides. ***The Heller method employs free field electrophoresis to transport analytes or reactants to selected micro-locations where they are effectively concentrated and reacted with the specific binding entities. Each micro-location of the Heller device has a derivatized surface for the covalent attachment of specific binding entities, which includes an attachment layer, a permeation layer, and an underlying direct current micro-electrode.*** The presence of ***the permeation layer prevents any electrochemically generated reagents from interacting with or binding to either the points of synthesis or to reagents that are electrophoretically transported to each synthesis site.*** Thus, ***all synthesis is due to reagents that are electrophoretically transported to each site of synthesis.***

Applicant respectfully submits that one of the major differences of the presently claimed method over the method taught by Heller *et al.* is the presence of electrochemically generated reagents according to the present methods. Applicant respectfully directs the Examiner's attention to claims 1 and 47 where the recitation of this feature is explicit in the claim language. In the interest of further clarifying the present invention and thereby advancing prosecution, Applicant herein amends the other broadest pending claims, namely claims 16 and 41. Applicant herein combines the language of

claims 16 and 17, and Applicant herein combines the language of claims 41 and 42. By way of this minor amendment, the broadest claims, namely claims 1, 16 and 41 now all recited the feature of electrochemically generated reagent. This feature is neither taught nor suggested by Heller *et al.* By explicitly reciting this feature in the claim language, Applicant clearly describes a method that is not anticipated by and that is not obvious over Heller *et al.* All of the remaining claims are patentable over Heller *et al.* for the simple reason that all the remaining claims depend from one of the independent claims among other reasons.

Applicant further set forth some of the limitations of the Heller *et al.* method and therefore some of the advantages of the presently claimed method. The method of Heller *et al.* is severely limited by the use of electrophoretic transport. First, electrophoretic transport requires that the reactants be charged in order to be affected by the electric fields; however, conventional reactants of interest for combinatorial chemistry are usually uncharged molecules not useable in an electrophoretic system. Second, the Heller method does not address the large amount of chemical crosstalk that inherently occurs because of the spatial distribution of the electric fields involved in the electrophoretic transport of the reagents for binding. In a system utilizing electrophoresis, one cannot use protecting groups to protect the reactive functional groups at the microlocations since there is no mechanism for removing the protective groups. The use of electrophoresis results in various binding entities and/or reactants being located throughout the solution used as they migrate, often coming into contact with unselected reaction sites. Thus, the combination of the lack of protecting groups and the spatial distribution of the electric fields inherent to electrophoresis allow such binding reactions to occur randomly, compromising the fidelity of any polymer being synthesized.

The presently claimed method provides an improved method for synthesizing a variety of chemical sequences at known locations that uses highly efficient deprotection and coupling mechanisms. The presently claimed method further provides a method for synthesizing a variety of chemical sequences at known locations that is cost-effective and

practical. In addition, the presently claimed method allows using a smaller sized apparatus affording more efficient production in a specific area and time while maintaining the fidelity of the chemical sequences produced.

In response to the present rejections, Applicants further submit that Heller *et al.* say nothing regarding electrochemical placement of any materials or compounds.

Respectfully, the Examiner is directed to Column 20, lines 25-48. The teachings set forth there only describe using electric fields to transport reagents. There is absolutely no mention of generating electrochemical reagents. Moreover, the electrodes involved are removed from the site at which the chemical reactions occur.

Additionally, regarding the further reasons stated regarding claims 2, 18, 43, and 48, Heller *et al.* may disclose buffering solutions, but the purpose is not to prevent electrochemically generated reagents from diffusing as set forth above.

Additionally, regarding the further reasons stated regarding claims 3, 19 and 49, the electrodes are distant from the microcapillary tubes of Heller's device. Additionally, regarding the further reasons stated regarding claims 4, 20 and 50, a buffer solution will not work in the apparatus and methods of Heller *et al.*

Additionally, regarding the further reasons stated regarding claim 39, Heller *et al.* describe circuitry that is external to and separate from the device. There is no teaching of a switch box.

Claim Rejections - 35 USC § 103

Heller *et al.* in view of Southern

The Examiner rejects claim 35 under 35 U.S.C. 103(a) as being unpatentable over Heller *et al.* as applied to claims 1-34, 36-44 and 47-51 above, and further in view of Southern U.S. Patent 5,667,667. According to the Examiner, although Heller *et al.* as applied, argued and disclosed above teach capping of unbonded deprotected chemical functional groups, they fail to expressly recite acetic anhydride or n-methylimidazole as the

capping agents. However, the Examiner maintains that this teaching is provided by Southern in Col. 7, lines 6-10 and lines 25-35 where capping agents similar in composition, function and result as those of Applicant's are disclosed. The Examiner states that it would have been obvious to a person of ordinary skill in the art at the time of the invention to have employed the use of highly sensitive dimethoxytrityl groups for capping unbonded deprotected chemical groups taught by Southern in the Heller *et al.* method because Southern has shown that these materials employed through sequential layering would have facilitated the overall method by allowing for modification of different regions of the surface of the substrate by application of different potential to relevant electrodes without the need for repositioning the electrode array, absent evidence to the contrary.

Applicants respectfully state simply that Southern does not disclose electrochemically generated reagents for the purpose of deprotecting. The dimethoxytrityl groups themselves are what are deprotected and removed in the teachings of Southern. Therefore, the agents mentioned by the Examiner are not used as capping agents. Hence, the deficiencies stated regarding Heller *et al.* are not cured by Southern.

Heller *et al.* in view of Savery

The Examiner rejects claims 45 and 46 under 35 U.S.C. 103(a) as being unpatentable over Heller *et al.* U.S. Patent 5,929,208 as applied to claims 1-34, 36-44 and 47-51 above and further in view of Savery U.S. Patent 4,280,885. According to the Examiner, while Heller *et al.* teach the use of an array of electrodes and a system of activation and deactivation of said electrodes for synthesis, they fail to expressly recite the use of a getter structure such as a ring-shaped electrode. However, the Examiner says that Savery teaches methods and applications for getter electrodes wherein the getter structures are spiral-like and are used to create electric fields that facilitate electrolytic processes effected on semiconductor substrates (col. 4, lines 5-15). The Examiner contends that it would have been obvious to a skilled artisan at the time of the invention to have employed

the getter structures taught by Savery in the Heller *et al.* method for electrochemical synthesis because Savery has shown that the getter structures would have facilitated the overall process by increasing the rate of electrolysis thus providing for a more efficient process, absent evidence to the contrary.

Applicants respectfully submit that Savery teaches an exposed electrode that is openly exposed to water. The water is not in the device itself. There are no electric fields created in the teachings of Savery. The electrode structure of Savery is intended to electrochemically electrolyze water. Further, it is meant to eliminate water that is present near a semiconductor device. Savery does not employ an electric field to “getter” ions. Rather, Savery uses electrochemistry to hydrolyze water.

Double Patenting Rejection

The Examiner provisionally rejects claims 1-51 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-49 of copending Application No. 09/003,075. Although the conflicting claims are not identical, the Examiner says that they are not patentably distinct from each other because Applicant's pre-amendment to independent claims 1, 16, 41, 44 and dependent claim 2 does not provide a clear demarcation between the claims of the instant and said copending. According to the Examiner, as the claims are read in light of the specification and as the specification provides for porous substrates, the instant claims are found to be within the scope of claims 1-49 of the parent application 09/003,075.

The Examiner provisionally rejects claims 1-51 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-51 of copending Application No. 09/394,138. Although the conflicting claims are not identical, the Examiner says that they are not patentably distinct from each other because Applicant's pre-amendment to independent claims 1, 16, 41, 44 and dependent claim 2 does not provide a clear demarcation between the claims of the instant and said copending. According to the Examiner, as the claims are read in light of the specification

and as the specification provides for porous substrates, the instant claims are found to be within the scope of claims 1-51 of co-pending 09/394,138.

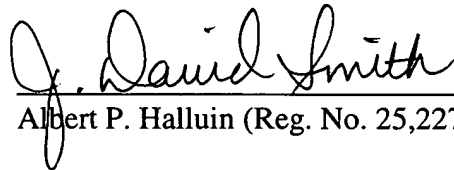
While Applicants do not acquiesce that either of the double patenting rejections are correct, Applicants submit their willingness to consider submitting a Terminal Disclaimer at the appropriate time.

CONCLUSION

Applicants submit that the claims are now in condition for allowance and earnestly seek rapid advancement as such. Should any questions arise in connection with this submission which may be resolved by a telephonic interview, the Examiner is invited to contact the undersigned at the telephone number listed below.

Respectfully submitted,

Date: July 27, 2000

 Reg. No. 39,839
Albert P. Halluin (Reg. No. 25,227)

HOWREY SIMON ARNOLD & WHITE, LLP
Box No. 34
1299 Pennsylvania Avenue, N.W.
Washington, D.C. 20004-2402
(650) 463-8100